Cancer immunotherapy

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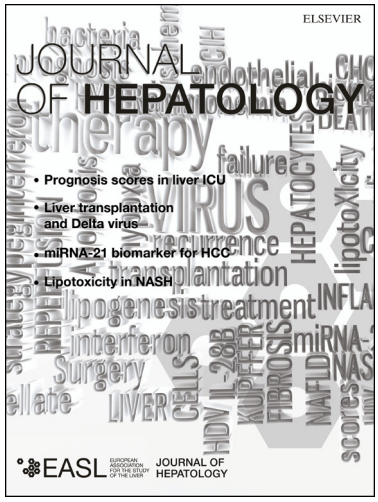

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Cancer Immunotherapy: Targeting the difference

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COMMENTARY ON:

Cancer Immunotherapy Based on Mutation-Specific CD4+ T Cells in a Patient with Epithelial Cancer. Tran E, Turcotte S, Gros A, Robbins PF, Lu YC, Dudley ME, Wunderlich JR, Somerville RP, Hogan K, Hinrichs CS, Parkhurst MR, Yang JC, Rosenberg SA. Science. 2014 May 9;344(6184):641-645. Reprinted with permission from AAAS.

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Abstract. *Limited evidence exists that humans mount a mutation-specific T cell response to epithelial cancers. We used a whole-exomic-sequencing-based approach to demonstrate that tumor-infiltrating lymphocytes (TIL) from a patient with metastatic cholangiocarcinoma contained CD4+ T helper 1 (TH1) cells recognizing a*

mutation in erbb2 interacting protein (ERBB2IP) expressed by the cancer. After adoptive transfer of TIL containing about 25% mutation-specific polyfunctional TH1 cells, the patient achieved a decrease in target lesions with prolonged stabilization of disease. Upon disease progression, the patient was retreated with a >95% pure population of mutation-reactive TH1 cells and again experienced tumor regression. These results provide evidence that a CD4+ T cell response against a mutated antigen can be harnessed to mediate regression of a metastatic epithelial cancer.

T cell based cancer immunotherapy, the concept of utilizing T cells to cure cancer patients was until recently regarded with skepticism. One of the main conceptual problem is that, physiologically, T cells recognize and eliminate cells that express non-self proteins. These are not usually present in cancer cells that instead express so called “tumor-associated antigens”, which are self-antigens expressed at different levels in cancer versus normal cells [1,2]. There are immunological consequences of this feature: tumor-associated antigens are poor inducers of tumor-specific T cells that do not expand in patients or poorly recognized the tumor cells. A second consequence is that if and when tumor-associated antigen-specific T cells are efficiently produced (for example by engineering T cells with chimeric T cell receptor (TCR) specific for tumor-associated antigens), the T cells will not only target tumor but also normal cells with clinical outcome that might be extremely severe [3]. However, the concept that cancerous cells do not express immunogenic non-self antigens change after the demonstration that the genetic alterations present in cancers can lead to production of new immunogenic “ non-self” antigens that can be exploited to induce effective tumor-specific T cell response. T cells specific for these

tumor-specific neo-antigens were detected in melanoma and were suggested to be the cause of the high immunogenicity of this cancer.

In this new paper, Tran *et al.,* makes the very important demonstration that such "neo antigens" are present and immunogenic not only in melanoma but also in cancer of epithelial origin which account for 80% of all human cancers. Furthermore, they not only demonstrated that T cell recognizing a mutated version of a tumor associated antigen can be detected in a patient with metastatic cholangiocarcinoma but also that these mutation-specific T cells unique to the patient's cancer can be harnessed to mediate regression of a metastatic epithelial cancer.

To demonstrate the presence of the mutation-specific T cells, the authors first used a leading-edge whole-exomic sequencing based approach to identify mutated candidate epitopes expressed on lung metastases of a patient with bile duct cancer not responsive to standard chemotherapy. The 26 detected mutated sequences were expressed on autologous antigen presenting cells using constructed libraries of minigenes encoding the mutated sequences. They then tested whether the patient's tumor-infiltrating lymphocytes (TIL) recognized any of these mutations and demonstrated that T cells infiltrating the patient's tumor comprised of T cells that recognized only a mutated version of a ERBB2-interacting protein (ERBB2IP) but were unresponsive to the wild type non-mutated ERBB2IP. These mutations-specific T cells were CD4 cells, HLA-DQB1*0601 restricted, recognized a minimal epitope composed of 13 amino acids and seemed to be of mono-oligoclonal origin since they were characterized for a very restricted TCR usage. Direct evidences that these mutation-specific T cells can be exploited for therapeutic purpose were obtained by showing that adoptive cell transfer of a large quantity (42.4 billion) of the expanded TIL, of which about 25% were CD4+ ERBB2IP mutation-reactive T lymphocytes

caused tumor regression and disease stabilization for approximately one year. This clinical efficacy was confirmed after a second round of adoptive T cell therapy in which 95% of the transferred cells were Vβ22+ ERBB2IP mutation-reactive TH1 cells that caused an accelerated tumor regression.

Therefore, by demonstrating that mutations present in epithelial tumors produced new antigens able to induce T cells that recognize the patient-specific mutated protein, Tran *et al* bring to the forefront an alternative strategy to generate T cells for adoptive cell therapy and treat patients with common epithelial cancers, where there is a low frequency of tumor-reactive T cells. The results presented in this study are also encouraging as CD4+ TH1 cells, other than CD8 CTL, can confer clinical benefit in targeting cancer.

Targeting sporadic or driver mutations unique to a patient's individual cancer with mutation-reactive T cells have also the advantage to cause minimal amount of "off-target" reactivity (cross-reactivity) and thus avoiding the severe side effects that have been described in some recent cancer immunotherapy trials [4,5].

Despite the remarkable results, the data has been obtained from a single patient and the feasibility of such method have to be evaluated in more patients with different epithelial cancers to analyze the extent to which tumor mutations can be targeted by adoptive T cell therapy. Furthermore, the approach described in this report is perhaps limited to cancers where there are few mutations, as screening hundreds of mutations for immunogenicity is technically challenging with current technology and there is also the risk that an already genetically unstable tumor might simply escape immune attack via down-regulation of the target protein. There have been evidence in human studies suggesting that effective immunotherapy might lead to cancer immunoediting [6,7]. Given the heterogeneity of majority of cancers, it is difficult to

predict if targeting a single mutation epitope might result in durable tumor control or selection of immunoresistant tumor variants that might accelerate tumor progression [8]. Nevertheless, the authors commented that “mapping of the mutational landscape of human cancer is occurring at rapid pace but clinical strategies to exploit such knowledge for clinical benefit remains to be realized”; and perhaps in the near future it might be possible to apply multi-epitope-based cancer immunotherapies in the clinic.

This pioneering work opens the new exciting possibility to develop real personalized immune based targeted therapy for many different cancers. Sequences of proteins expressed by tumors could be used to detect mutations or also the presence of other “non-self proteins” like for example viral antigens, that should be highly represented in hepatitis B virus (HBV)-related HCC (where a high frequency of HBV-DNA integration is known to occur) [9], and target them with T cells expanded from the tumors or engineered to express specific T cell receptors [10].

The experimental framework to translate such knowledge in new therapy has been provided. The realization of clinical benefits for cancer patients might not be such a distant reality.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Figure legend

Fig. 1. A schematic of identification of TIL that recognize patient-specific mutation in a patient with epithelial cancer, followed by treatment of patient using adoptive cell therapy with TIL containing Vβ22+ *ERBB2IP* mutation-reactive T cells.

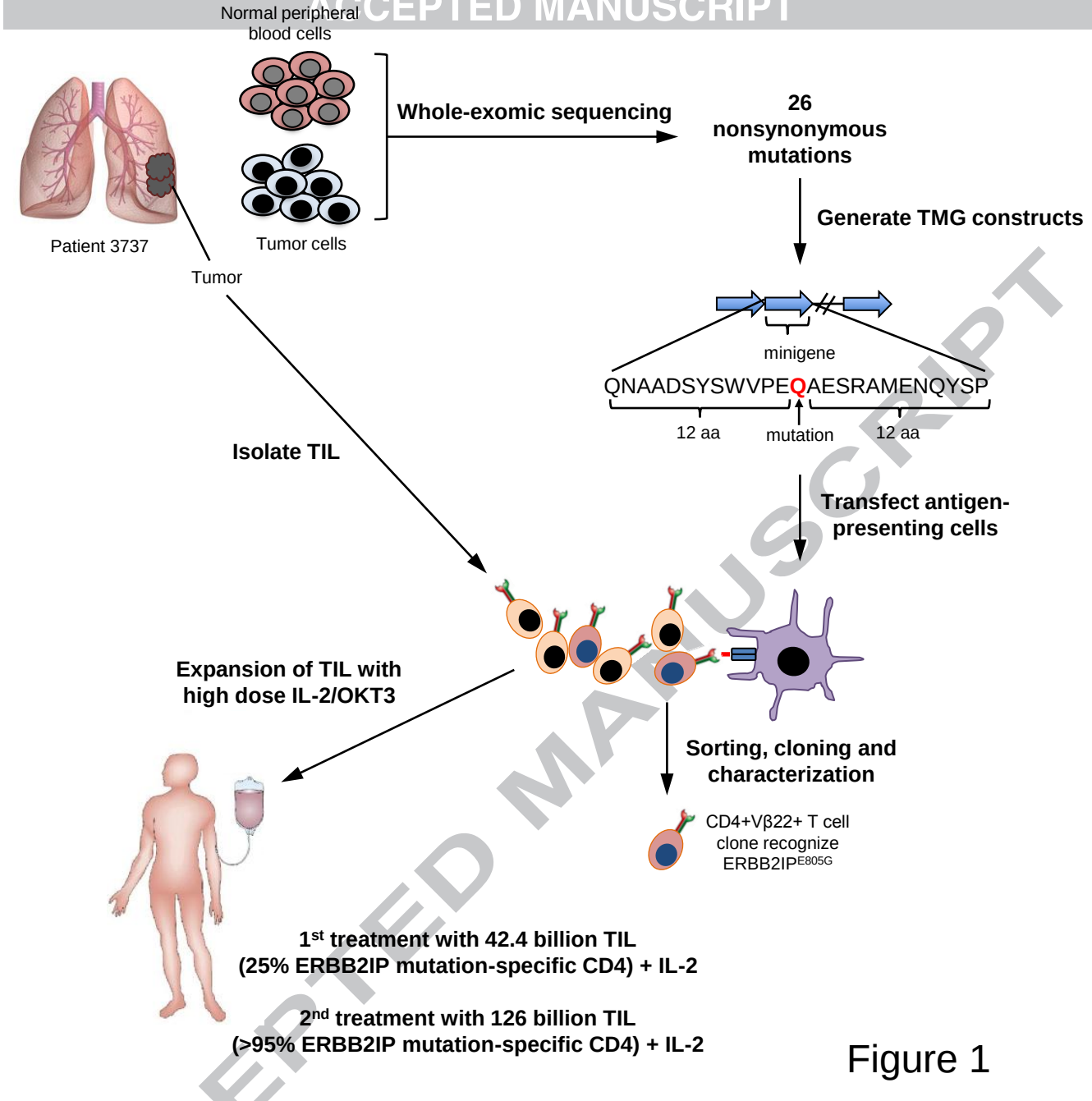

Figure 1